Long-Term Observations on Tubular and Glomerular Function in Cadmium-Exposed Persons

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Four groups of cadmium-exposed persons, from different workplaces and with different types of exposure, have been followed for periods of 9–20 years. In one group the total observation time is over 30 years, since they were included in Friberg's original study. The studies include determination of inulin or creatinine clearance, protein excretion and specific indicators of renal tubular dysfunction. The results indicate that once tubular dysfunction is established, it is irreversible, even when it is minor. In some persons it was noted that the development of renal dysfunction seemed to be a multistage process. The initial stage is characterized by an increased excretion of low molecular weight proteins like β_2-microglobulin and ribonuclease. After a period of several years with no or low exposure, there was a relatively sharp increase in excretion of total proteins and albumin and a decrease in glomerular filtration rate. This is interpreted as being the result of further increases in renal concentration of cadmium and in spread of cadmium along the tubules. Metallothionein absorption in the tubules, its catabolism and synthesis must play an important role for the development and progress of the tubular dysfunction. It was not possible to show that a decrease in glomerular filtration rate occurs before low molecular weight proteinuria.

Introduction

The renal dysfunction caused by cadmium is generally regarded as irreversible. Workers from the group originally studied by Friberg (1) in 1946 were subsequently subjected to several re-examinations (2–6). The first follow-up study was carried out by Friberg and Nyström in 1952 (2). These authors found that the proteinuria in the examined group had not disappeared; on the contrary, they found that proteinuria had developed in some subjects after cessation of exposure. In 1959, 39 of these workers were again re-examined (3), and it was found that there was practically no change in the results of qualitative tests using nitric acid, but the number of trichloroacetic acid-positives had increased. Further studies on workers from this particular group, using quantitative protein determinations, showed that at intervals of 6 months and 3 years, respectively, no major changes had taken place in urine protein excretion (4,5). A new follow-up in 1977 (6) showed

that of 18 workers a few had a further increase of protein excretion, but in most cases excretion rate was unchanged. In no case was there a normalization of urine protein excretion or of the electrophoretic pattern. Thus, even cases with moderate increase in total protein (100–200 mg/day) remained at that level. It has been claimed (7) that the proteinuria is reversible, but this finding was based on qualitative tests only.

By determination of inulin clearance, Friberg (1) found a decrease in glomerular filtration rate (GFR) in 19 workers subject to heavy exposure. These workers and several others were examined in 1959 and inulin clearance determined (8). A relationship between exposure time and decrease in inulin clearance was found.

Since 1959, most Swedish studies have focused on the tubular dysfunction and measurement of protein excretion. However, in several groups of workers, glomerular function has been studied since 1969 by determination of creatinine clearance, serum creatinine and serum β_2-microglobulin.

A number of separate studies have been performed in different industries where various

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types of cadmium exposure exist. In the present paper some preliminary data from these studies of interest to the discussion on mechanisms for and development of renal disease following cadmium exposure are discussed. An overview of these findings has recently been presented (9).

Materials and Methods

Four different groups of workers were studied. The first group consisted of seven workers exposed to cadmium oxide dust in a battery plant. They were first examined by Friberg in 1947 (1) and have subsequently been examined several times during the years 1959–1978. A second group consisted of 16 battery workers exposed to cadmium oxide dust, who were first examined in 1969 (10) and re-examined in 1982. The third group consisted of six workers in a copper–cadmium alloy producing plant. They were first examined in 1969 (10) and re-examined in 1981. The fourth group consisted of 11 men and 3 women. This group was exposed to cadmium dust during polishing of cadmium-plated candle holders for periods of a few months to 4 years. For all subjects exposure ceased in 1972, at which time the hazard was discovered. Repeated examinations were carried out in 1972 to 1975, and 1977 to 1979. During the latter period subjects were examined every fourth month.

The methods used for evaluation of tubular and glomerular function included; determination of creatinine in serum and urine (11), total protein (3), β_2-microglobulin (12) and ribonuclease (13). Electrophoretic analysis of concentrated urine proteins on paper (4) has been performed routinely since 1959. Urinary cadmium was determined by atomic absorption spectrophotometry (14).

Results

In the first group of seven workers, inulin clear-

Table 1. Clearance of inulin or creatinine in seven cadmium workers not subjected to heavy exposure to cadmium since 1950.

Case No.[a]	Age,[b] yr	Inulin, mL/min		Creatinine, mL/min		
		1947	1959	1959	1969	1978
16 (33)	67		111	79	52	53
18 (30)	72		77	68	—	50
27 (6)	70	106	121	83	85	66
32 (11)	73	132	72	96	—	68
35 (37)	82		112	65	71	49
36 (3)	71	78	99	87	61	34
38 (16)	69	79	111	83	66	48

[a]The same as in previous papers (3–6). Numbers in parentheses refer to Friberg (1).
[b]In 1978.

ance was determined for four workers in 1947. As can be seen in Table 1, both inulin clearance and creatinine clearance were determined in 1959, whereas in 1969 and 1978 only creatinine clearance was determined. Five laboratories used five different methods for the determination of glomerular filtration rate. Therefore, is not possible to make a quantitative evaluation of these data, but it is obvious that there must have been a considerable decrease in glomerular filtration rate over the years much more than can be accounted for by age.

Table 2 shows the results of quantitative determination of protein. Quantitative data on protein excretion are not available from 1947. However, in two cases, subjects 27 and 35, free electrophoresis of undiluted urines was performed, which indicates that protein excretion must have been considerable (1). With regard to electrophoretic patterns, there were no major changes in 1959 to 1978, except in case 16, where in 1959 the percentage of albumin was 10%, but during all later examinations was 22–23%. This change in electrophoretic pattern coincided with a large increase in protein excretion and probably also a considerable reduction in GFR, as is shown in Table 1.

Table 2. Total urine protein in seven men not subjected to heavy exposure to cadmium since 1950.

Case No.[a]	Age, yr[b]	Urine protein							
		mg/24 hr				mg/g creatinine			
		1959	1963	1969	1978	1969	1972	1975	1978
16	67	280	790	1230	1160	880	440	530	660
18	72	350	430	—	750	370	600	390	460
27	70	570	760	640	920	410	540	350	620
32	73	890	850	—	1400	—	—	960	840
35	82	1090	770	730	1110	630	—	790	1080
36	71	1100	1080	880	1280	810	910	980	1210
38	69	1300	—	1090	1400	750	870	740	850

[a]The same as in previous papers (3–6).
[b]In 1978.

Of the 16 workers in the second group, four had cardiovascular diseases with a considerable intake of drugs, e.g., cardiac glycosides and hypertensive drugs. These four workers were treated separately. In six workers, mean age 65 years, with normal clearance of β_2-microglobulin in 1982, it was seen that there had been virtually no change in serum creatinine or creatinine clearance over a period of 13 years (9.2–9.5 mg/L and 120–124 mL/min, respectively). These workers also had a normal excretion of ribonuclease in 1969 and of total protein in 1969 and 1982. The urinary excretion of cadmium was, on the average, 6 μg/g creatinine in 1982.

Six workers, mean age 64 years, had an increased relative clearance of β_2-microglobulin in 1982. In this group there were already in 1969 signs of tubular disease since both total protein and ribonuclease excretion were increased. However, the glomerular filtration rate also was already lower than in the normal group (106 mL/min) in 1969. The urinary excretion of cadmium was on an average 10.7 ug/g creatinine in 1982. Over a period of 13 years there was an increase in serum creatinine, from 10.1 to 12 mg/L, indicating a decrease in glomerular filtration rate, but clearance determinations did not verify this, that, being 106 and 99 mL/min, respectively. The largest changes were seen in the group with cardiovascular disease with a considerable reduction in glomerular filtration rate, from 116 to 81 mL/
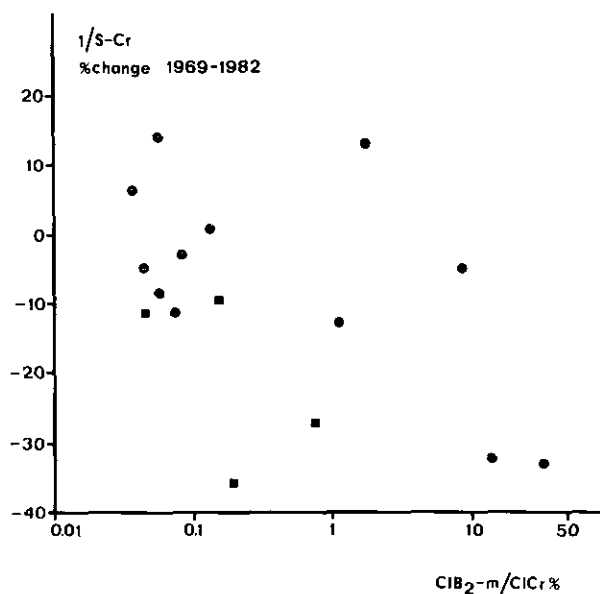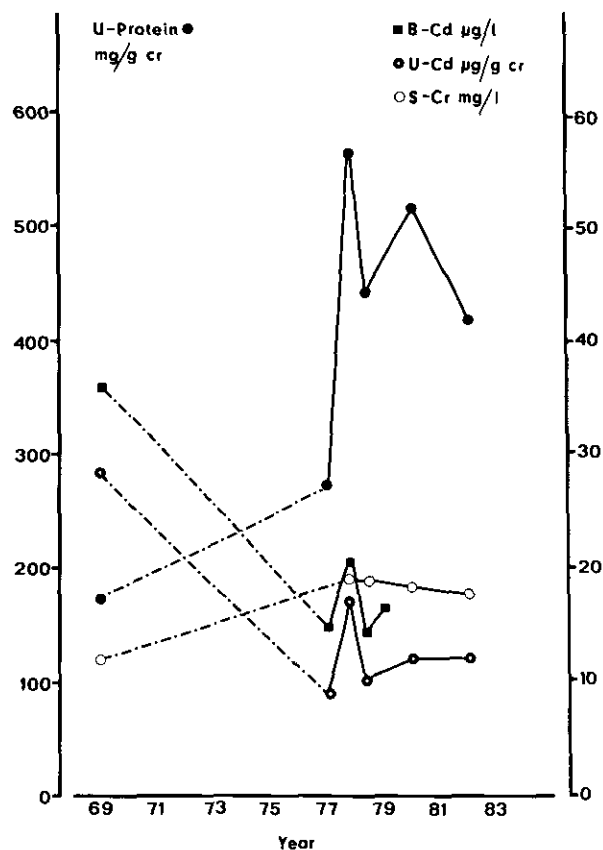

FIGURE 2. Changes from 1969 to 1982 in blood and urine cadmium, serum creatinine and urine protein in a cadmium worker. The dashed lines from 1969 to 1977 indicate the uncertainty about changes during that period.

min. However, the clearance of β_2-microglobulin was only sightly elevated in this group.

In Figure 1, the change of the reciprocal of serum creatinine, which is proportional to the decrease in glomerular filtration rate, is plotted against the relative clearance of β_2-microglobulin. It will be seen that only in two cases, with a marked increase in clearance of β_2-microglobulin, is there a considerable reduction in glomerular filtration rate, whereas in cases with moderate increase in relative clearance of β_2-microglobulin it is not possible to show any trend for a decrease in filtration rate. More details on these findings are to be found elsewhere (9).

In one case data were also obtained on renal function in 1977, 1978 (two observations) and 1980. Figure 2 shows that, whereas there was a considerable reduction in blood and urine cadmium from 1969 to 1977, there was a moderate increase in urine protein. From 1977 to 1978 there was a sharp increase in total protein, accompanied by moderate increases in blood and

FIGURE 1. Changes in glomerular filtration rate from 1969 to 1982 in relation to relative clearance of β_2-microglobulin in 1982 in 16 cadmium workers. The squares represent four workers with severe cardiovascular disease.

urine cadmium. Serum creatinine was about 50% higher in 1978 than in 1969, but unfortunately it was not determined in 1977.

In 1969, electrophoresis showed moderate tubular proteinuria, and in 1977 tubular proteinuria with low albumin and a large β_2-microglobulin peak. By 1978 the pattern had changed to a "classic" tubular pattern with about 20% albumin.

The third group from the cadmium-copper alloy factory consisted of six persons only. Four of these had normal clearance of β_2-microglobulin, and two had an increased clearance rate. The two latter cases have shown a significant reduction in creatinine clearance since 1969. The largest reduction was, however, seen in one person with normal β_2-microglobulin clearance and normal protein excretion and a normal electrophoretic pattern. The urinary cadmium in this case was 6 µg/g creatinine. It has not been possible yet to obtain more data on this person which would make it possible to evaluate whether there is a relationship to cadmium exposure or some other cause for the change in clearance.

In the fourth group, repeated examinations were made over a period of 28 months. Since analysis was repeated on stored samples after termination of the study, quite reliable estimates were obtained for creatinine and β_2-microglobulin in serum and urine, as well as for cadmium in blood and urine. Some data from these studies have been reported elsewhere (9,15). Three persons who displayed the highest cadmium excretion also had small but significant increases in the relative clearance of β_2-microglobulin. In two of these cases there was also an increase in total protein excretion. The dose-response curve was of the hockey-stick type, i.e., no effect could be seen at cadmium levels below 5 µg/g creatinine in urine. The increases in β_2-microglobulin excretion appeared to occur at about 6 µg/g creatinine. During the study period there was no general trend toward increases or decreases in serum levels of creatinine or β_2-microglobulin. In one woman an increase in serum creatinine was demonstrated. However, in this particular case no increase was seen in serum β_2-microglobulin. A slow but continuous increase in urine protein and urinary β_2-microglobulin was seen, and this woman also began to excrete more cadmium when protein excretion increased.

Conclusions and Summary

These preliminary data indicate that there is a slow progression of the renal dysfunction in cad-

mium workers. It was not possible to find evidence of glomerular function being affected earlier than tubular function. In some cases with originally moderate proteinuria, more rapid changes were observed later, as can be seen in Table 2 and Figure 2. In these cases the protein excretion as well as the albumin content of the urine proteins increased after peak exposure. This fact stresses the need for examination even after cessation of exposure or a decrease in exposure. It is conceivable that the initial defect is at that site in the proximal tubule where metallothionein is initially reabsorbed. High local concentrations of metallothionein and cadmium in the tubular cells will eventually influence the reabsorption of β_2-microglobulin. Cadmium will spread upwards or downwards in the tubule, and eventually the reabsorption sites for more anionic proteins like albumin or cationic proteins like lysozyme will be affected. This means that there is a multistage process, depending on at what stage the local critical concentrations are reached in the different segments of the proximal tubule. It is also possible that, depending on intensity of exposure, the metallothioneins delivered to the renal tubules may vary in charge, which may lead to small changes in absorption rates.

It is obvious that more knowledge about metallothionein metabolism and cadmium transport is needed to validate these speculations.

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